CDER Office of Compliance
Office of Drug Security, Integrity & Recalls
Division of Import Operations & Recalls
Imports Exports Compliance Branch

FDA compliance focal point for imports & exports of CDER regulated drugs

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Day 2

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Imports Exports Compliance Branch Mission: To promote and protect the public health by ensuring drug importation and exportation adhere to FDA standards of compliance.

PLAIR

(Pre-Launch Activities Importation Request)

- FDA's policy to exercise enforcement discretion on the importation of a limited amount of an unapproved finished dosage form drug product in preparation for the market launch based upon anticipated approval
- Drug product may require minimal further processing such as final packaging and/or labeling
- Drug Product may be in final packaged form
- CDER regulated NDA, ANDA or BLA

- Does not apply to bulk ingredients or pending supplements.
- Draft Guidance for Industry (pending)

PLAIR

Background:

- Section 505(a) of the FD&C Act prohibits the introduction of any new drug into interstate commerce unless there is an approved application filed for that drug.

- FDA may exercise enforcement discretion to permit the introduction into interstate commerce of certain unapproved finished dosage form drug products.

- Firm(s) not following the PLAIR procedures will be subject to normal entry procedures.

Where to submit a PLAIR and how to obtain PLAIR information

- A PLAIR can be submitted by email on a PDF compatible format to CDER-OC-PLAIR@fda.hhs.gov mailbox only. This mailbox is also used to provide PLAIR information upon request.

What should be included in a PLAIR?

- Drug product name (complete product description)
- Application (NDA, ANDA, BLA) number
- Name of CDER's application project manager of the pending application
- NDC (National Drug Code) – if assigned
- Name, address, registration #, telephone # of the foreign drug product manufacturer; US consignee; warehouse or distribution facility owned or under contract with the applicant
- A letter signed by an authorized representative of the applicant certifying various conditions.

When should a PLAIR be submitted?

- **NDA** –no more than 60 days before the user fee goal date for completion of the review of the pending application for approval

- **ANDA**- no more than 60 days prior to expected approval

What happens after a PLAIR is submitted?

- Receipt confirmation is issued to the applicant
- CDER IECB reviews the PLAIR submission
- Check GMP status of foreign manufacturer
- Follow-up with OND for NDAs and BLAs or OGD for ANDAs for any CMC deficiency

The overall review process for the PLAIR can take up to two weeks.

CDER Office of Compliance may exercise enforcement discretion to either:

- **Grant the PLAIR** – CDER notifies the firm by email with instructions to follow.

- A copy of granted PLAIR is communicated to ORA/DIO. The firm then provides DIO in advance with the import entry number.

  Note: the firm must be registered per 510(i) but drug listing per Sec. 510(j) is not a requirement until the drug product has received approval and is ready for commercial distribution.

- **Deny the PLAIR** – due to one or more of the following reasons:

- Manufacturer(s) are not in compliance with CGMPs
- Application deficiencies
- PLAIR is too premature

When a PLAIR is denied, the firm does not need to resubmit the PLAIR but may follow up within 30-45 days of submission.

Who are the main contacts?

CDER:

CDER-OC-PLAIR@fda.hhs.gov

ORA/Division of Import Operations:

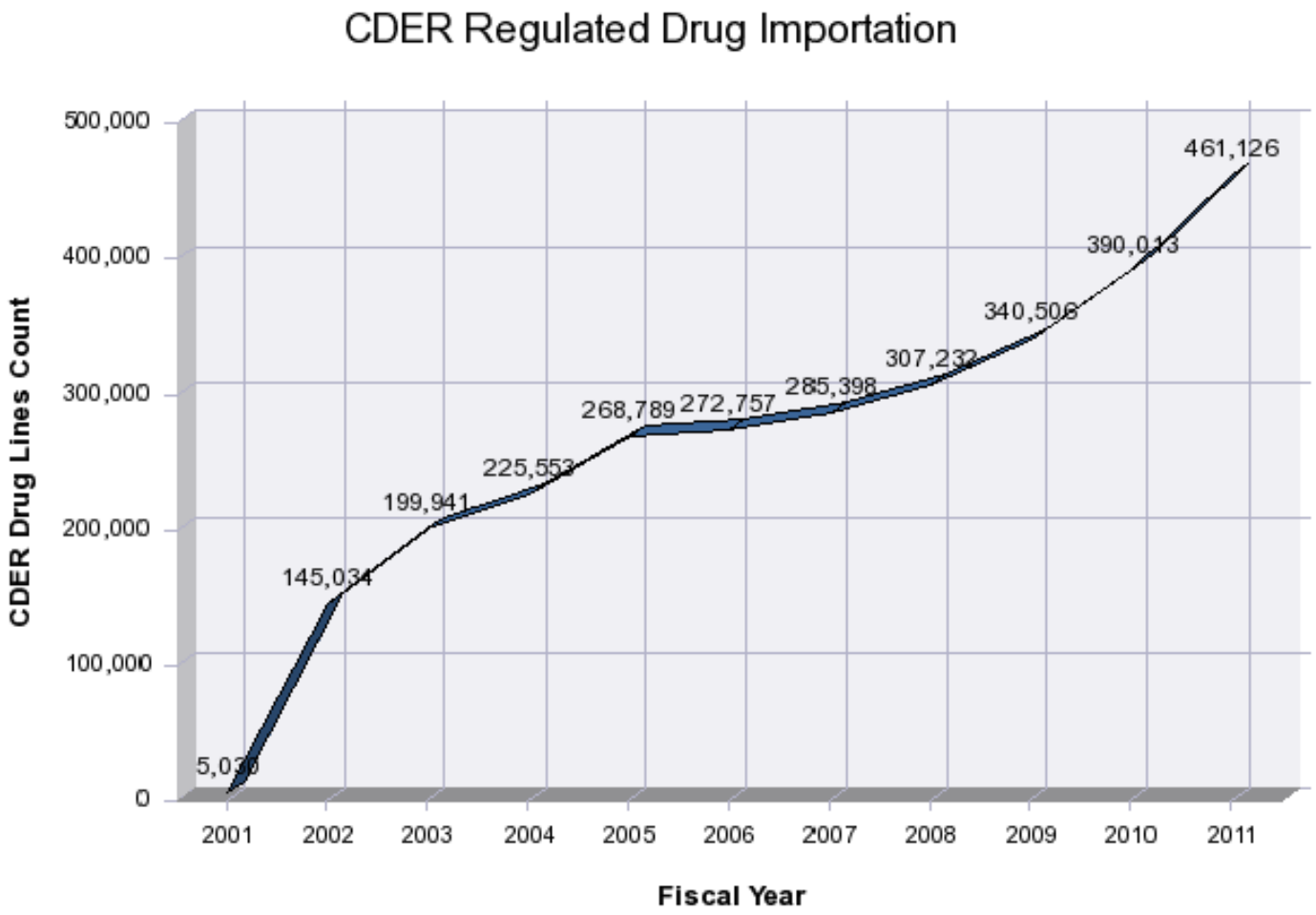
DIOPPLAIR@fda.hhs.gov

General Drug Imports Requirements

Recognize various drug imports requirements:

- Registration and Listing Requirements
- Labeling
- Marketing requirements for OTC and Rx Drugs
- Addressing Adulteration
- Misbranding & Adequate Directions for Use
- Importation of Drug Products (finished dosage form) and Active Pharmaceutical Ingredient (API)
- Diversion of imported APIs

Ten Years of Drug Imports



Imports Admissibility

- Administrative Detention and Hearing Process
  - Happens at the District level (see 21 CFR 1.94)
  - Notice of FDA Action
  - 766 reconditioning certain misbranded drugs into compliance
  - Unapproved new drugs may not be brought into compliance see RPM Chapter 9:

    "Do not permit the relabeling of a drug detained on a new drug charge as a means to bring the item into compliance."
- Products not brought into compliance are refused
- Refused articles must be destroyed or exported
- If the drug poses a health hazard, FDA and Customs & Border Protection (CBP) may request restricted redelivery.

Drug Imports

CUSTOMS HOUSE BROKER (CHB)/FILER

ABI

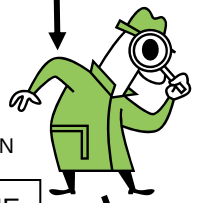
ACS/ PRIOR NOTICE

OASIS (PREDICT)

FDA HOLD

DISCLAIMED

- LABEL
- CONTAINER INTEGRITY
- SAMPLING
- VERIFICATION

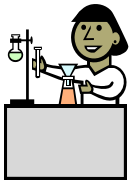


MAY PROCEED

EXAMINE

SAMPLE

LAB



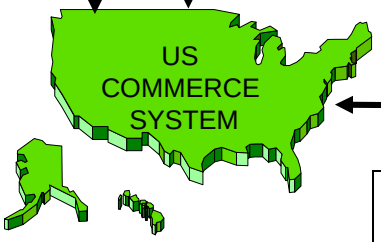
LAB REPORT

RECOMMEND DETENTION

DATA

DATA

DATA



RELEASE

COMPLIANCE OFFICER

CUSTOMS & BORDER PROTECTION

REFUSED

DETENTION & "TESTIMONY"

~ 90 days

EXPORT

DESTRUCTION

NOTICE OF FDA ACTION: DETENTIONS AND REFUSALS

Entry Review Decisions

Five decisions may result from the imports entry review process*

(1) may proceed (not Automatic)
(2) request additional information for further evaluation
(3) refer to District Compliance Branch
(4) field examination
(5) sample collection

*At any point District Office can contact Headquarters for assistance

Definition: "Drug" *[FDCA 201(g)(1)]*

Drug is an article …

- Intended to diagnose, cure, mitigate, treat or prevent disease in man or other animals
- Intended to affect the structure or any function of the body of man or other animals (other than food)
- Recognized in the United States Pharmacopeia/National Formulary, Homeopathic Pharmacopeia of the United States or any supplement to the said lists
- Intended for use as a component of a drug

Definition: "New Drug" *[FDCA 201(p)]*

- "any drug ... the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience..., as safe and effective (GRAS/E) for use under the conditions prescribed, recommended or suggested in the labeling"
- A “new drug” must be covered by an approved new drug application (NDA/ANDA) to be marketed in the U.S. or by an investigational new drug application (IND) *[FDCA Section 505]*
- Applies to both Rx and OTC drugs

Drug or Device

- When a firm submits a device listing it is required to state why the product is not a drug (see FDCA 510(j)(1))
- Combination products (21 CFR 3.2(e))
- Convenience kits containing both are required to meet both regulatory requirements

CDER New Drug Approval (NDA/ANDA)

- Product, firm, manufacturer, label specific
- Firm submits data on safety and efficacy
- FDA evaluates data, approves or does not approve the drug
- Every firm must seek FDA approval for any drug product requiring FDA approval

Approved new drug must be:

1. Manufactured, packaged, or labeled at a facility covered in the application using the formulation and process approved
2. Manufactured using an API supplied by a manufacturer covered in the application

Definition: Prescription (Rx) drugs

[FDCA 503(b)(1)]

Drugs that cannot be used safely without medical supervision.

- Examples?
  - Injectable* drugs
  - Drugs to treat serious conditions like heart disease, cancer, or fertility issues

*Generally, injectable drugs are Rx, but insulin is not Rx in every state.

Drug Label Requirements

Per FDCA, all drugs must bear:

- 502(b) – The name & place of manufacturer, packer, or distributor (also see 21 CFR 201.1)
- 502(b)(2) – Accurate statement of the quantity of contents 502(c) – Must be understandable, must be in English (also see 21 CFR 201.15)
- 502(e) – Established name and quantity of each active ingredient (also see 21 CFR 201.10)

Drug Label Requirements

- Adequate directions for use (21 CFR 201.5)
- 502(f)(1) – Misbranding and exemption from charge
  - Drug products, that is, finished dosage form Rx drugs are exempt when they meet all labeling conditions at 21 CFR 201.100
  - APIs are exempt from misbranding when they meet certain labeling requirements

Active Pharmaceutical Ingredient (API)

[21 CFR 207.3(a)(4)] a.k.a. bulk drug substance

"any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, **becomes an active ingredient or a finished dosage form of the drug…**"

"term does not include intermediates used in the synthesis of such substance"

- Lyophilized drugs such as hGH and hCG are finished drugs, not APIs – Require NDA approval

Registration: Domestic & Foreign

- FDCA 510(b), (i) – Registration Requirements
  - Manufacturers: API & finished drug products
  - Repackers and relabelers
  - Control laboratories: registration only
  - Domestic manufactures that pack/repack, label/relabel, etc. drugs under the Import for Export (IFE) requirements

- NO ESTABLISHMENT REGISTRATION?
  - Drug is misbranded under FDCA 502(o)

Foreign Firm Registration & Drug Listing [FDCA Sec. 510 & 21 CFR 207]

All foreign firms that manufacture, prepare, propagate, compound, or process a drug imported or offered for import into the U.S. shall, through electronic means …

- Register the name and place of business
- Designate a U.S. Agent
- Provide names of each known importer & person who imports or offers for import
- List all drug products imported or offered for import into the U.S.

Drug Listing: Requirements

- FDCA 510(j) – Drug Listing
- NO or INADEQUATE DRUG LISTING?
  - Drug is misbranded under 502(o) and subject to refusal under section 801(a)(3).
- NDC Numbers
  - FDA requests but does not require NDC appear on the product label or labeling
  - If NDC appears on the label it must comply with regulation at 21 CFR 207.35 (b)(3)

Registration & Listing

- Listed products: assigned National Drug Code number (NDC #)
- NDC # format identifies the following:
  - Labeler code: manufacturer or distributor
  - Product code: drug formulation
  - Package code: trade package size and type
- Registration or Listing does not indicate FDA's approval of firm or products [21 CFR 207.39]

Affirmations of Compliance

AofC: NDA, NDC, DLS, REG, CFR, UFC, etc.

Test Question:

I provided a valid NDC number so the drug is approved:

(T)rue

(F)alse

I provided a valid NDC number therefore:

(a) The firm is adequately registered and drug is listed

(b) The drug can be marketed

(c) The drug is an investigational drug

Affirmations of Compliance

I provided a valid firm registration number therefore the drug is listed:

(T)rue

(F)alse

The active pharmaceutical ingredient (API) has a different listing from the finished dosage form listing number:

(T)rue

(F)alse

Imported Drugs

Under section 801(a) of the act, an article (drug) is subject to refusal if it appears from examination or otherwise:

(1) It has been manufactured, processed, or packed under unsanitary conditions

(2) Forbidden or restricted for sale in the country in which it was produced/exported

(3) Is adulterated, misbranded, or in violation of section 505 of the act

801(a)(3)

- Adulteration (FFDCA 501)
  - GMP issues
- Misbranding (FFDCA 502)
  - Lack of adequate directions for use or evidence of qualification for exemption
- Violation of 505
  - new drugs without an application
  - this includes INDs

Adulteration & Imports

- cGMP and inspection status [501(a)]
  - Investigational new drugs
  - Pre-approval products
- Labeling
  - 501(b) monograph or compendial
  - 501(c) non-monograph or compendial
- Analysis (certificates or testing)
  - 501(d) reduction in quality or substitution

Intended Use

- How many intended uses can I claim for my imported drug?
- How many labels can my imported drug have?
- Explanation or statement of intended use, intended use letters, etc.

  API – Active Pharmaceutical Ingredient

  Drug Product – a finished dosage form Rx or OTC drug

API/bulk drug labeling and 502(f)(1) Misbranding Exemptions

Before your firm can label an API your firm must qualify to label the API.

Your firm may qualify if you can demonstrate the intended finished product is not a new drug.

21 CFR 201.122

- *201.122(a):* API intended for use in a product **approved** in NDA, ANDA, or supplement
- *201.122(b):* API intended for use in product **subject** to an IND
- *201.122(c):* API intended for use in product subject to a **pending/near** NDA or ANDA or supplement approval

API Exemptions from Misbranding
[21 CFR 201.122(a)]

- Intended for use in a product **approved** in a NDA or ANDA
- Manufactured by the firm qualified in the new drug application
- Intended for use in **approved** prescription (Rx) and/or over-the-counter (OTC) drugs

API/Bulk Drug Exemptions
[21 CFR 201.122(a)]

Labeling must have the statement:

- "Caution: for manufacturing, processing, or repacking"
- "Rx only" – if in all dosage forms in which the bulk drug may be used is subject to a human prescription *[503(b)(1)]*

API/Bulk Drug Exemptions from Misbranding cont… *[21 CFR 201.122(a)]*

Useful Information upon entry*:

- API name and NDC number
- Name and address of the API manufacturer
- Number of approved NDA/ANDA or supplement
- Intended finished dosage drug product name and NDC number

* Useful Information that may demonstrate applicability of an exemption. Alternative information may also suffice.

API/Bulk Drug Exemptions Summary *[21 CFR 201.122(a)]*

- API must be labeled per *21 CFR 201.122*
- Intended finished product must be covered by **approved** application or supplement
- API must be from a supplier **approved** in the application/supplement

Supplements & Pending Application

- NDA/ANDA sponsors must ensure with CDER reviewers reason is inputted in the comments folder why application or supplement is pending
- If no reason, then we reserve the authority to assume product cannot be released due to safety and efficacy reasons
  - Major reason for entries being detained
- Foreign OAI Inspections: Entry is not released

OAI: Official Action Indicated (gross CGMP violations)

CGMP: Current Good Manufacturing Practices (21 CFR 210 & 211)

Useful Information

(API Information not in Establishment Evaluation System)

Useful Information:

1. APIs included in original or initial application:

- Copy of the documents from original submission showing the supplier of the API (e.g. CMC information with drug substance information)
- Explain any discrepancies (e.g. change in name or address)
- FDA Approval Letter

2. APIs included in a supplement:

- Copy of the official FDA letter approving the supplement and covering the API supplier
- Explain any discrepancies (e.g. change in name or address)

API for Pre-Submission Batches
[21 CFR 201.122]

Application Pre-Submission Batches

- Drug used to conduct the studies needed to generate data required to submit an application or supplement
- FDA may exercise enforcement discretion

Useful Information to submit upon importation:

- Explanation of API intended use
  - Example: Bioequivalence and/or bioavailability batches.

APIs for Pre-Submission Batches cont … *[21 CFR 201.122]*

Useful Information – Cont.:

- API name and NDC #
- Name and address of the API manufacturer
- Name and address of U.S. consignee
- Must be labeled as per *21 CFR 201.122*
- For supplements - may include NDA/ANDA number to be supplemented and NDC # of finished product

Submit requests to cderimportsexports@fda.hhs.gov

API for OTC Drugs: Pending & Final Monographs

Labeling (Must State):

- "Caution: for manufacturing, processing, or repacking"
- Useful Information to provide upon importation:
  - Name and NDC # of product to be manufactured with the API
  - A statement justifying why an approval is not required for the finished drug product
  - API label content demonstrating compliance with *21 CFR 201.122*

Imported API Summary

API may be exempt from misbranding if:

- meet certain labeling requirements
- are not used to manufacture a finished drug that is an unapproved new drug*
- are manufactured by a supplier approved in the new drug application/supplement or included in a pending application/supplement

* Exempted by regulations or granted enforcement discretion

APIs - Adequate Directions for Use

Summary

APIs may be imported to manufacture…

- Prescription (Rx) and over-the-counter (OTC) drugs subject to approved or pending applications or supplements
- Rx drugs not currently subject to application requirements
- OTC drugs subject to pending and final OTC monographs

801(d)(1) & PDMA

- Drug products subject to FDCA 503(b) may be re-imported only by the original manufacturer (no exemptions)
- Definition of Manufacturer for this purpose is restricted to the person who performs all of the following operations (see 21 CFR 201.1):
  - Mixing, Granulating, Milling, Molding, Lyophilizing, Tableting, Encapsulating, Coating, Sterilizing, and Filling sterile, aerosol, or gaseous drugs into dispensing containers

Import for Export (IFE) [801(d)(3)]

- Section 322 of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Public Law 107-188

- Signed into law on June 12, 2002, and amended section 801(d)(3) of the FDCA.

- Allows importation of violative articles of drug, i.e., misbranded, adulterated, and unapproved, if the importer provides certain information to FDA at the time of the initial importation into the United States.

Import for Export (IFE) [801(d)(3)]

- Provided importer affirms in writing that imported drugs will be further processed into products to be exported by the initial owner or consignee in accordance with section 801(e) or section 802 of the Act.

- FDA must be provided with certain information:
  - Written statement article (finished dosage form or API) is to be further processed, and the resultant manufacture, processor, packer, distributor or any entity that had possession of the article
  - CoA to identify the article
  - Records when requested

Import for Export (IFE) [801(d)(3)]

- Must execute a bond for any liquidated damages
- Must maintain records of use and/or destruction
- Must destroy any article not used in production

- Article can be refused admission if credible evidence that it is not intended to be further processed
- Prohibited Acts [301(w)]: Exempts exportation
  - False information and statement
  - Introduction into interstate commerce any article (including finished)
  - Not submitting and maintaining records and COA

Foreign Trade Zone (FTZ)

- CBP's designation to exempt from payment of duties, taxes, bonds. Considered by CBP to be outside U.S.
- Articles not offered for consumption, thus not considered "imported or offered for import".
- If in FTZ, subject to FDA laws since considered within the "territory" of the U.S.
- 801 does not apply until article is out of FTZ
- Introducing unapproved new drugs into FTZ violates new drugs [505(a)] and prohibited [301(d)]
- Can bring into FTZ articles of drug (bulk or finished) pending approval

Exporting Drugs [FDCA 801]

Criteria to legally export drugs:

(A) meet the specifications of the foreign purchaser;

(B) not be in conflict with the laws of the country to which they are intended for export;

(C) be labeled on the outside of the shipping package that they are intended for export; and

(D) not be sold or offered for sale in U.S. domestic commerce

Exporting Drugs [FDCA 801(e), 802]

- Legally marketed articles of drug in the U.S. have no exportation restrictions
- Articles manufactured specifically for export only may be exported & cannot be marketed in the U.S. [801(e)(1)(D)]
- Articles manufactured specifically for U.S. found to be adulterated, misbranded, or unapproved cannot be exported
- Must keep records (21 CFR 1.101)*

Export Certificates

- FDA issues export certificates
- CDER issues CDER regulated drug export certification per FDCA 801(e)(4)
- $175 for the first certificate for product exported from US
- Information? Please contact us at:

  cderexportcertificateprogram@fda.hhs.gov

FDASIA Title VII

New Authorities and Mandates

- 701 Registration of domestic drug establishments (FDCA 510(b))
- 702 Registration of foreign establishments (FDCA 502(o), 510(i))
- *703 Identification of drug excipient information FDCA 510(j))*
- 704 Electronic registration and listing (FDCA 510(p))
- *705 Risk-based inspection frequency (FDCA 510(h))*
- 706 Records for inspection (FDCA 704(a))
- *707 Prohibition against delaying, denying, limiting, or refusing drug inspection (FDCA 501))*
- 708 Destruction of adulterated, misbranded, or counterfeit drugs offered for import (FDCA 801(a))

FDASIA Title VII

New Authorities and Mandates (continued)

- *711 Enhancing the safety and quality of drug supply (FDCA 501)*
- *712 Recognition of foreign government inspections (FDCA 809)*
- *713 Standards for admission of imported drugs (FDCA 801)*
- *714 Registration of commercial importers (FDCA 801)*
- *715 Notification (FDCA 301)*
- *716 Protection against intentional adulteration (FDCA 303)*
- 717 Penalties for counterfeiting drugs (18 USC)
- 718 Extraterritorial jurisdiction (FDCA 301)

DRUG Import Alerts

55-03: Detention Without Physical Examination (DWPE) of Different Forms of Heparin and Heparin-Related Products for CGMP Issues

55-05: DWPE of finished dosage drug products, active pharmaceutical ingredients, and inactive ingredients for potentially hazardous microbiological contamination

62-05: Sterile drugs from facilities not inspected by FDA

66-40: Drugs manufactured in violation of GMPs

66-41: Unapproved New Drugs

66-66: Misbranded APIs

66-72: Unapproved/misbranded drugs- CDER initiative on Rx drugs marketed w/o approval

99-34: Drug and Device Firms without a valid drug or medical device firm registration

End

- Thank you!
- Email questions to:

  cderimportsexports@fda.hhs.gov